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Short Communication
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Antibiotic Development and Clinical Utilization; A Reality Check

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Short Communication

The global significance of Antimicrobial Resistance (AMR) has been recognized by several bodies including the United Nations and World Health Organization [1,2]. In fact, the medical profession has been alerting us for almost 20 years with the IDSA coining the term "bad bugs no drugs" [3]. The pharmaceutical industry has had a mixed response to the situation. Several multinational companies have simply walked away from antibiotic research and development so the small, often single drug program, firms have tried to fill this major and growing gap. It is true that there have been no new drug classes for about 20 years and that the new candidate drugs are simply extensions of what we already have. This is largely correct but some new drugs have the potential to be "game-changers".

It is important to appreciate the significant hurdles to pharmaceutical companies to develop new antibiotics imposed by the regulatory agencies. Most notable is the clear difference between the US FDA and the EMA in Europe in terms of the endpoint chosen to establish efficacy i.e. infection site specific versus pathogen specific [4,5]. There are other differences but none as significant as this one. What it means is that totally different studies need to be completed to satisfy each authority. This contributes to the large and ever-increasing costs of creating and approving a new antibiotic without the ability to ever re-coup these costs once approved.

In the 2000's, methicillin-resistant *Staphylococcus aureus* was an emerging major pathogen with increasing morbidity and mortality being reported. This species became one of the main causes of skin infections. One particular worry was the significant emergence of MRSA in the community setting, thus moving the emphasis of therapy to the out-patient setting or at least the emergency care unit. This pathogen became the focus of several companies with different approaches to the problem. Drugs such as linezolid and daptomycin were novel molecular approaches, but then there were significant modifications on well-established molecules which could treat the problems of skin infections and provide positive healthcare changes. These new agents included the cephalosporin, ceftaroline and the glycopeptide derivatives of vancomycin; dalbavancin, telavancin and oritavancin.

In 2012 there were 3.3 million skin infections in the US [6] while 358,212 patients were hospitalized in the Kaiser Health system alone due to their infection [7]. Various studies have shown that *S aureus* causes >50% of skin infections and at least half of these are MRSA. Indeed, Suaya [7] estimated that being hospitalized with a *S aureus* skin infection will cost $11,000 per patient. Clearly, avoidance of hospitalization or early hospital discharge is preferred provided efficacy and safety are maintained.

The complex interface between providing the best healthcare in the right setting at the right price has become more challenging as bacterial resistance continues to increase, healthcare system budgets are tightened and the need to discharge patients sooner for both economic and quality of life reasons. A great proportion of skin infections are treated with traditional agents such as vancomycin which are still considered adequate. However, use of data beyond the standard registration trials is needed for formularies to review practices to include new alternative drugs. This data is often referred to as "real world".

Real-World Studies (RWS) document the actual care that patients receive in the clinic and involve a diversity of patient cases (e.g., patients suffering from several comorbid diseases at the same time) without the limitation of strict inclusion and exclusion criteria seen in phase 3 studies.

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These RWSs may generate long-term data on effectiveness and safety of health interventions while giving useful insight for health economic analyses. These studies are not perfect as issues such as the lack of standardized data collection, the lack of data quality standards, the lack of representative databases or the lack of enough studies demonstrating how RWS can be used in healthcare systems [8].

The management of skin infections is particularly appropriate for assessment in the real-world setting, as the standards of care are well established, if not always well quantified. Use of new therapies could support changes to the current protocols by either avoiding hospitalization once diagnosed in the emergency room, primary care setting or enable early discharge from hospital when otherwise well but still on IV antibiotics.

All current regimens employ duration of therapies of 7-14 days. Some can be intravenous (IV) and/or utilizing a step-down approach to oral therapy, but patient adherence is uncertain. In attempts to fulfill the previous objectives of hospital avoidance or early discharge as well as not increasing overall healthcare costs, the long-acting lipoglycopeptide molecules were modified to yield three new related class members. All are approved for use in skin infections and two have had real world analyses undertaken to ascertain the true value of these single or short dose treatments, dalbavancin and oritavancin. Dalbavancin and oritavancin have very long half-lives, >200 hours, and are active against MRSA along with various other skin organisms. In two randomized, double-blind trial, adults with SSTI were administered either a single intravenous 1200-mg dose of oritavancin or 7-10 days of twice-daily vancomycin. Efficacy endpoints that were tested for non-inferiority included primary composite endpoint at 48-72 hours and ≥20% reduction in lesion area at 48-72 hours. Both studies showed oritavancin to be non-inferior to vancomycin. Clinical response in trial 1 was 82.3% for oritavancin and 78.9% for vancomycin (CI 3.4 (-1.6; 8.4) and trial 2 80.1% compared to 82.9% (-2.7 (-7.5; 2.0). With regard to reduction in lesion size, non-inferiority was shown [9].

Intravenous dalbavancin was initially studied using a two-dose regimen given 7 days apart with the option to switch to oral linezolid to complete 10 to 14 days of therapy. The primary end point was early clinical response, required the cessation of spread of infection-related erythema and the absence of fever at 48 to 72 hours. In the pooled analysis, 525 of 659 patients (79.7%) in the dalbavancin group and 521 of 653 (79.8%) in the vancomycin-linezolid group had an early clinical response indicating treatment success (weighted difference, -0.1 percentage point; (95% confidence interval, -4.5 to 4.2) [10]. Subsequently, to eliminate the need for patients not returning for the second infusion, a single dose of dalbavancin was studied and has been shown to be non-inferior to two doses of the drug [11]. Several studies of both dalbavancin and oritavancin have been reported predominantly in skin infections but have included prosthetic joint, osteomyelitis and diabetic foot infections [12-15]. The use of these once weekly options for longer course of therapy infections like prosthetic joints and osteomyelitis would not only potentially decreases hospital admissions, but also prevents the need for a PICC or midline catheter, which in turn could decrease central line infections.

Dalbavancin

There have been two recent studies of dalbavancin in the real-world setting [16,17]. Although the first was focused on skin infections, the second includes other Gram-positive infections. A retrospective chart review evaluated adults diagnosed with acute skin and skin structure infections treated with IV antibiotics in which patients received either dalbavancin or conventional therapy [16]. In-hospital baseline demographics as well as outpatient clinical variables and outcomes were assessed. The primary outcome was the total Infectious Disease (ID)-related cost of care per patient. One hundred and fifty-eight patients were enrolled. Sixty-four received dalbavancin and ninety-four received conventional therapy. The total ID-related cost of care per patient was greater with dalbavancin (mean $4,561) compared to conventional therapy (mean $1,668), $p < 0.01$. In the subset of patients treated with daptomycin, the total ID-related cost (mean $5,218) was comparable to dalbavancin (mean $4,561). The authors [16] concluded that dalbavancin was more costly than conventional therapy for the outpatient treatment of ABSSSI. This greater overall cost was likely driven by the higher acquisition cost of dalbavancin. However, dalbavancin may be comparable to the daily use of daptomycin for ABSSSI [16]. A second study [17] employed multi-center, retrospective database review of all patients receiving dalbavancin in 16 Physician Owned Infusion Center (POICs) during July 2014 to March 2015. Demographics, therapy characteristics, microbiology, Adverse Events (AEs), clinical outcomes and recurrences were evaluated. Dalbavancin was administered to 105 pts with 57 (54%) males and an overall mean age of 62 ± 16 years. The main diagnoses were cellulitis (45%), abscess (28%), osteomyelitis (12%), diabetic foot infection (11%) and implanted prosthetic device infection (4%). Forty-nine pts (47%) had dalbavancin therapy initiated in the POIC and 56 pts (53%) received dalbavancin following hospitalization. Fifty-five pts (53%) received other intravenous antibiotics prior to treatment with dalbavancin for a median of 5 days. Eighty-seven pts (83%) received 2 doses of dalbavancin, one week apart. Six pts (6%) received more than 2 doses. Infusions were administered by peripheral intravenous catheter in 84 pts (80%). Eighty-one patients yielded positive cultures, methicillin-resistant *S. aureus* was the most frequent pathogen (48%). Overall clinical success was reported in 88 of 105 pts (84%) with 52% cured and 32% improved. Reasons for failure included disease exacerbation in 6 patients (6%) and serious adverse events causing discontinuation of dalbavancin in ten pts (9%). Of these, 9 of 10 patients had hypersensitivity reactions following the first dose, the majority (67%) occurring in patients receiving other parenteral antibiotics prior to dalbavancin. Mild to moderate AEs were reported in 20 pts (19%), most commonly diarrhea (n = 10), nausea (n = 4), dizziness (n = 4) and infusion site reactions (n = 3). Disease recurrences within 60 days post dalbavancin therapy occurred in 7 of 82 evaluable pts (9%). The authors reported that out-patient use of dalbavancin appears to be safe and effective although adverse events were notable, including those requiring dalbavancin discontinuation. The use of dalbavancin may offer added safety and potential cost reductions in this setting due to avoidance of central line catheters. In addition, for patients that require longer durations of therapy past 14 days, the half-life of long-acting lipoglycopeptides allows for at least one week less of dosing compared to a traditional agent, which in turn, dramatically saves cost to the patient and healthcare system [17].

Oritavancin

There have been several reports of the use of oritavancin in the real-world setting in which the avoidance of hospitalization or early hospital discharge were studied. A retrospective evaluation of two Truven Health Market scan Databases which contained patients covered by private health care plans from large companies and other

patients covered by Medicare [18]. The purpose of this study was to compare the 30-day hospital admission rates and health care costs among patients with SSTI's who received oritavancin (n = 120) or vancomycin (n = 6695) in the outpatient setting [18]. Patients were comparable at baseline for a range of demographic and pre-clinical characteristics, prior antibiotic therapies, type and site of the skin infections, severity of the infections, and prior use of health care (hospitalization, emergency room visit, and outpatient care as three example factors), as well as health care costs. Multivariate analysis showed that patients who received single-dose oritavancin were significantly less likely to be hospitalized, compared to those who received multi-dose vancomycin (5.8% *vs* 16.2%; P = 0.002). The mean ± standard deviation 30-day cost of treatment between the oritavancin and vancomycin patient groups was $10,096 ± $8865 vs $12,779 ± $28,773; P = 0.3. These results support the rationale for single-dose oritavancin as an alternative to multi-dose vancomycin for the treatment of ABSSSI.

Whittaker et al. [19] undertook a retrospective analysis during May 2017-January 2018, of in-patients with SSTI which evaluated the clinical and economic comparison of the two regimens, vancomycin and oritavancin. Medical records were reviewed and data collected including demographics, medical history including previous skin infections and length of hospital stay. An analysis of financial data was conducted for patients based on their DRG and reimbursement using specific hospital system expenditures. A total of 101 patients were enrolled, 50 received vancomycin at the standard dosing and 51 received oritavancin, 1200 mg single dose. The 2 groups were comparable in age and gender. More immunocompromised patients were seen in the vancomycin group, 20 *vs* 15, but the opposite was seen with IV drug abusers, 24 *vs* 14 oritavancin and vancomycin respectively. Notably, the length of hospital stay was significantly shorter in the oritavancin cohort, 3.3 days *vs* 5.6 (p < 0.001). Additionally, fewer patients were re-admitted in the oritavancin group, 2 *vs* 9 (p 0.0279). The economic implications of these outcomes were calculated based on the two groups using the overall costs. Overall it was estimated that use of oritavancin enabled an earlier discharge from hospital for the small groups evaluated was $217,206. Thus, despite the higher acquisition cost of oritavancin, the savings of 2.3 days per patients with all the other components actually saved expenditure.

Turner et al. [20] conducted a multicenter retrospective study of use of oritavancin to avoid hospital admission. Healthcare resource utilization and clinical response were the two outcomes. A total of 115 patients were enrolled with a mean age of 59.7 years, 93% had at least one comorbidity, such as diabetes, hypertension etc. and 61.7% were obese. In most cases this was the first presentation of a skin infection, 81.7%. Cellulitis was the most common type of infection with the legs being the most frequent site.

The success rate at 13.2 days (mean 6.5 days) was 99.1% with 83.2% still a success at follow up. In terms of healthcare resource utilization, six patients received diagnostic testing as part of their index visit. Twenty-six patients (22.6%) underwent a surgical procedure. Hospital admission occurred in seven patients of which three were infection related. Eleven patients required antibiotics in the 30 day follow up period. Interestingly the dominant subgroups admitted to hospital were aged >65 years, BMI >25kg/m^2, and diabetes, but MRSA and methicillin susceptible *S aureus* were no different in admission frequency. The cost of outpatient oritavancin was estimated to be $3,698 (mean) with hospital admission for SSTI estimated to be $6,823 (mean). Previous studies have calculated mean hospital costs for management of SSTI to be about $5,000 for outpatient dalbavancin and almost $7,000 for general inpatient admission for SSTI. The authors [20] concluded that oritavancin yielded a high clinical success rate and low rate of infection related 30-day readmission. These findings may provide an opportunity to manage these common infections in the outpatient setting.

Another interesting study [21] evaluated the overall effectiveness of oritavancin at a community hospital. Over the period 2015-2016, sixty-seven patient's records were examined. Most were male, 61% with a mean age of 52.3 years. Cellulitis accounted for almost 50% of infections. 90% were treated in the outpatient setting. No patients were re-admitted within 14 days, but 8 patients returned to the emergency department with infection related condition. Additionally, the financial benefit of treating cellulitis with oritavancin was calculated. By assuming the avoidance of a 6.6 day hospital stay, the amount estimated saved per patient was $9,753. The authors applied this estimate to their annual cases of skin infections, demonstrating that appropriate use of oritavancin to prevent admissions for ABSSTIs has the potential to save their hospital an estimated $653,451 annually. Moreover, the authors concluded that use of a single dose of oritavancin could avoid hospitalizations and enable earlier discharge from hospital. Both are cost saving applications [21].

A real-world analysis evaluated oritavancin in the out-patient setting use for SSTI reviewed 118 patients at a single site over a 10-month period [22]. Patients received either oritavancin or local Standard of Care (SoC) which included IV daptomycin (58%), dalbavancin (25%) and vancomycin (5%). Unsurprisingly 93.2% of patients had at least 1 comorbidity but only 3.4% were febrile. Clinical effectiveness was assessed at 5-30 days typically about 17 days. The clinical cure rate was higher in the oritavancin group 73.2% *vs* 48.4% in the SoC cohort (p = 0.03). Mean total costs were lower for oritavancin compared with SoC ($4035 *vs* $6354 p = 0.01) representing per patient savings of $2319. They concluded that their real-world study showed comparable efficacy rates to the phase three studies used to approve the compound but included more challenging patients [22]. The validity of phase three clinical trials in daily management of skin infections is modest, thus real-world studies are needed to truly understand how a new treatment modality such as single dose therapy may be best placed to provide optimal care for these common infections. Lodise et al. [18] estimated that 94% of all hospitalized SSTI did not have a life-threatening infection suggesting that over 500,000 hospital admissions could be avoided by out-patient use of single dose oritavancin. Data for dalbavancin and oritavancin clinical efficacy was similar between phase three studies and real-world analyses, however the latter permitted further assessments of healthcare resource utilization and overall economic implications which would not have been feasible from regulatory studies. In most settings, the comparator regimen was vancomycin with all its attendant issues such as therapeutic drug monitoring, central catheter related issues, and adverse events. Oritavancin was demonstrated to achieve savings from both the avoidance of hospital admission and early discharge from hospital. Barriers include inpatient formularies, changing standard practices of providers, and insurance approval for various treatment approaches all prove to be the biggest limitations to move forward even with real world data available. Hopefully as novel treatment therapies to infections are introduced, it will be feasible, and encouraged to undertake analyses of their impact in the actual clinical setting.

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